# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>11 January 1999 (11.01.99) | |
| **International application No.**<br>PCT/NL98/00259 | **Applicant's or agent's file reference**<br>PCT 0694 |
| **International filing date** (day/month/year)<br>11 May 1998 (11.05.98) | **Priority date** (day/month/year)<br>12 May 1997 (12.05.97) |
| **Applicant**<br>QUAX, Paulus, Hubertus, Andreas et al | |

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   11 December 1998 (11.12.98)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|---|
| **The International Bureau of WIPO**<br>**34, chemin des Colombettes**<br>**1211 Geneva 20, Switzerland** | Authorized officer<br>Nicola Wolff |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

Copy for the designated Office (DO/US)

PCT/NL98/00259

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

# PCT

## NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

SMULDERS, Th., A., H., J.
Vereenigde Octrooibureaux
Nieuwe Parklaan 97
NL-2587 BN The Hague
PAYS-BAS

**Date of mailing** (day/month/year)
28 September 1998 (28.09.98)

**Applicant's or agent's file reference**
PCT 0694

**IMPORTANT NOTIFICATION**

**International application No.**
PCT/NL98/00259

**International filing date** (day/month/year)
11 May 1998 (11.05.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
NEDERLANDSE ORGANISATIE VOOR TOEPAST-NATUURWETENSCHAPPELIJK ONDERZOEK TNO

State of Nationality: NL
State of Residence: NL
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
NEDERLANDSE ORGANISATIE VOOR TOEGEPAST-NATUURWETENSCHAPPELIJK ONDERZOEK TNO

State of Nationality: NL
State of Residence: NL
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

**The International Bureau of WIPO**
**34, chemin des Colombettes**
**1211 Geneva 20, Switzerland**

Facsimile No.: (41-22) 740.14.35

Authorized officer
Yolaine CUSSAC

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | FOR FURTHER ACTION | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
|---|---|---|
| PCT 0694 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/NL 98/ 00259 | 11/05/1998 | 12/05/1997 |

Applicant

NEDERLANDSE ORGANISATIE VOOR TOEGEPAST- ET AL

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL 98/00259

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-15 18 19

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5, 13-15 completely and 18,19 partially

A vector useful for transfection of mammalian cells comprising a nucleic acid insertion encoding an expressible hybrid polypeptide which comprises a domain with a binding function and a domain with an effector function, said binding function comprising a receptor binding domain and said vector is selected from the group of viral and non-viral vectors especially an adenovirus or a retrovirus vector and its use.

2. Claims: 6-12 completely and 18, 19 partially

A vector useful for transfection of mammalian cells comprising a nucleic acid insertion encoding an expressible hybrid polypeptide which comprises a domain with a binding function and a domain with an effector function, said effector function comprising an enzymatically active domain or a protease inhibitor activity and its use

3. Claims: 16-17 completely and 18, 19 partially

A vector useful for transfection of mammalian cells comprising a nucleic acid insertion encoding an expressible hybrid polypeptide which comprises a domain with a binding function and a domain with an effector function, wherein said nucleic acid insertion is under the control of a cell- or tissue-specific promoter and its use

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 98/00259

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N9/72 C12N15/62 C07K14/81 //C07K19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 96 34009 A (RUTGERS THE STATE UNIVERSITY OF NEW JERSEY) 31 October 1996 see page 10, line 10 - page 20, line 2 --- | 1,13-15, 18,19 |
| X | WO 91 12328 A (FOWLKES DANA M ET AL) 22 August 1991 * the whole document, esp. page 1-2 and page 28, line 20 - page 39, line 26 * --- | 1 |
| X | WO 96 23814 A (CELL GENESYS INC) 8 August 1996 see page 9 - page 10 --- | 1,18 |
| X | EP 0 383 599 A (MERCK & CO INC) 22 August 1990 see the whole document --- -/-- | 1-3,6,19 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 19 February 1999 | 09. 03. 99 |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Authorized officer<br>De Kok, A |

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 95 28955 A (GLIEMANN JOERGEN ET AL)<br>2 November 1995<br>see the whole document | 1,3 |
| A | WO 95 11987 A (INCYTE PHARMA INC)<br>4 May 1995<br>see page 25, line 4 - page 27, line 13<br>see page 85, line 10 - page 87, line 17 | 1-5,7,<br>18,19 |
| A | WO 92 02553 A (DELTA BIOTECHNOLOGY LTD)<br>20 February 1992<br>cited in the application<br>see page 3, line 10 - page 9, line 1 | 1-5,7,8,<br>11,18 |
| X | WO 95 17885 A (RUTGERS , THE STATE UNIVERSITY OF NEW JERSEY) 6 July 1995<br>see page 7, line 7 - line 10<br>see page 15, line 1 - page 23, line 36<br>see page 32, line 1 - page 34, line 6 | 1,7,8 |
| A | | 2-5 |
| P,X | WO 97 25422 A (NISSIN FOOD PRODUCTS LTD)<br>17 July 1997<br>cited in the application<br>see abstract | 1-5,7 |
| P,X | QUAX P H A ET AL: "Inhibition of neointima formation in cultured human saphenous vein segments by an adenovirus expressing an urokinase receptor binding plasmin inhibitor"<br>CIRCULATION,<br>vol. 96, no. 8-Suppl., 21 October 1997,<br>page I669 XP002084540<br>us<br>see abstract nr.: 3741 | 1-5,<br>13-15,<br>18,19 |
| X | EP 0 439 954 A (SERAGEN INC) 7 August 1991<br>see page 1 - page 4 | 1,6 |
| X | WO 97 00949 A (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 9 January 1997<br>see page 6, line 27 - page 7, line 6<br>see page 12, line 26 - page 13, line 17 | 1,6 |
| X | US 5 504 001 A (FOSTER DONALD C)<br>2 April 1996<br>see column 3, line 5 - line 55 | 1,6 |
| A | WO 88 09344 A (CREATIVE BIOMOLECULES INC)<br>1 December 1988<br>see abstract | 1,6 |

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 95 13091 A (INTERNATIONAL TECHNOLOGY MANAGEMENT ASS ) 18 May 1995<br>see abstract | 1,6 |
| A | EP 0 404 750 A (WASHINGTON UNIVERSITY)<br>27 December 1990<br>see abstract | 8,12 |
| A | WO 95 21601 A (PROTEIN ENGINEERING CORP.)<br>17 August 1995<br>see page 4, line 15 - page 5, line 24 | 8,12 |
| A | EP 0 623 676 A (AMGEN INC )<br>9 November 1994<br>see page 1 - page 4 | 1,8,12 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/NL 98/00259

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9634009 A | 31-10-1996 | US 5843724 A | 01-12-1998 |
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| WO 9112328 A | 22-08-1991 | CA 2075974 A | 16-08-1991 |
| | | EP 0515516 A | 02-12-1992 |
| | | JP 5503430 T | 10-06-1993 |
| | | US 5498538 A | 12-03-1996 |
| | | US 5747334 A | 05-05-1998 |
| | | US 5625033 A | 29-04-1997 |
| | | US 5852167 A | 22-12-1998 |
| | | US 5844076 A | 01-12-1998 |
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| | | DE 69025211 T | 19-09-1996 |
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| | | GR 3019836 T | 31-08-1996 |
| | | HK 15597 A | 14-02-1997 |
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| | | JP 7106159 B | 15-11-1995 |
| | | JP 2510846 B | 26-06-1996 |
| | | JP 7278200 A | 24-10-1995 |
| | | NO 300595 B | 23-06-1997 |
| | | PT 93178 A,B | 31-08-1990 |
| WO 9528955 A | 02-11-1995 | AU 2342995 A | 16-11-1995 |
| WO 9511987 A | 04-05-1995 | AU 685187 B | 15-01-1998 |
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| WO 9202553 A | 20-02-1992 | GB 2246779 A | 12-02-1992 |
| | | AU 8318591 A | 02-03-1992 |
| WO 9517885 A | 06-07-1995 | US 5550213 A | 27-08-1996 |
| | | AU 1515295 A | 17-07-1995 |
| WO 9725422 A | 17-07-1997 | AU 1210797 A | 01-08-1997 |
| | | EP 0890638 A | 13-01-1999 |
| EP 0439954 A | 07-08-1991 | AU 657087 B | 02-03-1995 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/NL 98/00259

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
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| | | CA 2071969 A | 23-06-1991 |
| | | JP 5502880 T | 20-05-1993 |
| | | WO 9109871 A | 11-07-1991 |
| | | US 5668255 A | 16-09-1997 |
| WO 9700949 A | 09-01-1997 | US 5726050 A | 10-03-1998 |
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| | | AU 648591 B | 28-04-1994 |
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| | | US 5482858 A | 09-01-1996 |
| | | US 5476786 A | 19-12-1995 |
| | | US 5132405 A | 21-07-1992 |
| | | US 5091513 A | 25-02-1992 |
| | | US 5258498 A | 02-11-1993 |
| WO 9513091 A | 18-05-1995 | AU 1176595 A | 29-05-1995 |
| EP 0404750 A | 27-12-1990 | AT 109796 T | 15-08-1994 |
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| | | EP 0739355 A | 30-10-1996 |
| | | JP 9511131 T | 11-11-1997 |
| | | US 5795865 A | 18-08-1998 |
| EP 0623676 A | 09-11-1994 | AT 170560 T | 15-09-1998 |
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| | | EP 0398753 A | 22-11-1990 |
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| | | SG 48766 A | 18-05-1998 |
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| | | WO 9014363 A | 29-11-1990 |
| | | US 5714465 A | 03-02-1998 |

PATENT COOPERATION TREATY

# PCT



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| PCT 0694 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/NL98/00259 | 11/05/1998 | 12/05/1997 |
| International Patent Classification (IPC) or national classification and IPC<br>C12N9/72 | | |
| Applicant<br>NEDERLANDSE ORGANISATIE VOOR TOEGEPAST...et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 10/12/1998 | 11.08.99 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. (+49-89) 2399-0 Tx: 523656 epmu d<br>Fax: (+49-89) 2399-4465 | Authorized officer<br>SCHEFFZYK, I<br>Telephone No. (+49-89) 2399 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL98/00259

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

| | | | | | |
|---|---|---|---|---|---|
| 1-23 | as originally filed | | | | |

**Claims, No.:**

| | | | | | |
|---|---|---|---|---|---|
| 1-17 | as originally filed | | | | |
| 18-21 | as received on | 25/06/1999 | with letter of | 25/06/1999 | |

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 3,4,5,9-12,15,17-19 |
| | No: | Claims | 1,2,6-8,13,14,16,20,21 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-21 |
| Industrial applicability (IA) | Yes: | Claims | 1-19 |
| | No: | Claims | 20,21: see section VIII/2). |

2. Citations and explanations

**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

SECTION V----------

Nucleic acid molecules according to claims 1, 13, 14 and 16 are already taught in WO 96/34009 (1) (see e.g. claims 2 and 28, page 16, line 21 and page 17, last paragraph). Moreover, the method claimed in claim 20 also is anticipated by the teaching of (1) (see e.g. claim 28).
Thus, claims 1, 13, 14, 16 and 20 do not meet the requirements of Art. 33(2)(3) PCT.

The same applies to the subject-matter of claims 2, 6-8 and 21 which is anticipated by the disclosure of WO 95/17885 (2) (see e.g. page 7, lines 1-10, page 27, first paragraph, page 30, second paragraph, page 33, third paragraph and claim 34). Moreover, for the sake of completeness it is noted that (2) is also detrimental to novelty of claims 1 and 20.

Claims 3, 4, 5, 9-12, 15, 17-19 appear to be novel since the embodiments thereof are not taught in the available prior art.

However, these claims cannot be considered to be inventive: the provision of nucleic acid constructs comprising sequences encoding a hybrid protein comprising a cell surface receptor binding domain and a domain with protease inhibitor activity to inhibit migration of tumor cells is already taught WO 92/02553 (3). Presently claimed constructs essentially differ from the construct described in (3) in that the vector encoding the hybrid protein is suitable to transfect mammalian cells whereas according to the teaching of (3) the hybrid protein is recombinantly produced in yeast. However, this difference merely can be considered as an obvious alternative to a person skilled in the art, in particular taking into account that the use of animal cells for said purpose is expressly suggested in (3) (see page 10, first paragraph) and, in addition, considering that the expression of hybrid proteins comparable to those defined in present claims , i.e. which comprise a binding domain and an effector domain in mammalian cells was well-known at the filing date of present application (see e.g. wo 96/23814 (4), example 2).

Therefore, the subject-matter of present claims do not meet the requirements of

Art. 33(3) PCT.

SECTION VI--------

Quax P. et al., Circulation, vol. 96, no. 8-Suppl., 21.10.97. page I669

WO 97/25422 priority date 08.01.96, filing date 06.01.97, publication date 17.07.97

SECTION VIII----------

1). The expression "pMAD5" used in claim 15 appears to be only an internal designation and thus renders the scope of said claim unclear (Art. 6 PCT).

2). For the assessment of the present claims 20 and 21 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

sub AA2

21. A process for producing a hybrid polypeptide or protein which comprises a domain with a binding function and a domain with an effector function, comprising transfecting or transducing mammalian cells with a recombinant nucleic acid molecule as claimed in any one of Claims 1 to 19 to obtain expression of the hybrid polypeptide or protein encoded by said nucleic acid molecule, and optionally recovering the hybrid polypeptide or protein produced.

insert AA3

add AA4

CLAIMS

18. A recombinant nucleic acid molecule comprising a vector useful for transfection or transduction of mammalian, e.g. human, cells, wherein said vector contains a nucleic acid insertion encoding an expressible hybrid polypeptide or protein which comprises a domain with a binding function and a domain with an effector function, wherein the domain with a binding function is a cell surface receptor binding domain.

19. A recombinant nucleic acid molecule comprising a vector useful for transfection or transduction of mammalian, e.g. human, cells, wherein said vector contains a nucleic acid insertion encoding an expressible hybrid polypeptide or protein which comprises a receptor binding domain selected from the group consisting of urokinase receptor binding domain of urokinase, receptor binding domain of epidermal growth factor, receptor associated protein that binds to LDL Receptor related protein ($\alpha_2$-macroglobulin receptor) and VLDL Receptor, and a domain with protease inhibitor activity which comprises a protease inhibitor or active part thereof, said protease inhibitor being selected from the group consisting of (bovine) pancreatic trypsin inhibitor, (bovine) splenic trypsin inhibitor, urinary trypsin inhibitor, tissue inhibitor of matrix metalloproteinase 1, tissue inhibitor of matrix metalloproteinase 2, tissue inhibitor of matrix metalloproteinase 3, and elastase inhibitor.

Subs AA1

20. A process for preventing local proteolytic activity, extracellular matrix degradation, cell migration, cell invasion, or tissue remodeling, comprising transfecting or transducing the cells involved or cells in their environment with a recombinant nucleic acid molecule as claimed in any one of the preceding Claims to obtain local expression of the hybrid polypeptide or protein encoded by said nucleic acid molecule.

AMENDED SHEET

21. A process for producing a hybrid polypeptide or protein which comprises a domain with a binding function and a domain with an effector function, comprising transfecting or transducing mammalian cells with a recombinant nucleic acid molecule as claimed in any one of Claims 1 to 19 to obtain expression of the hybrid polypeptide or protein encoded by said nucleic acid molecule, and optionally recovering the hybrid polypeptide or protein produced.

CLAIMS

18. A recombinant nucleic acid molecule comprising a vector useful for transfection or transduction of mammalian, e.g. human, cells, wherein said vector contains a nucleic acid insertion encoding an expressible hybrid polypeptide or protein which comprises a domain with a binding function and a domain with an effector function, wherein the domain with a binding function is a cell surface receptor binding domain.

19. A recombinant nucleic acid molecule comprising a vector useful for transfection or transduction of mammalian, e.g. human, cells, wherein said vector contains a nucleic acid insertion encoding an expressible hybrid polypeptide or protein which comprises a receptor binding domain selected from the group consisting of urokinase receptor binding domain of urokinase, receptor binding domain of epidermal growth factor, receptor associated protein that binds to LDL Receptor related protein ($\alpha_2$-macroglobulin receptor) and VLDL Receptor, and a domain with protease inhibitor activity which comprises a protease inhibitor or active part thereof, said protease inhibitor being selected from the group consisting of (bovine) pancreatic trypsin inhibitor, (bovine) splenic trypsin inhibitor, urinary trypsin inhibitor, tissue inhibitor of matrix metalloproteinase 1, tissue inhibitor of matrix metalloproteinase 2, tissue inhibitor of matrix metalloproteinase 3, and elastase inhibitor.

20. A process for preventing local proteolytic activity, extracellular matrix degradation, cell migration, cell invasion, or tissue remodeling, comprising transfecting or transducing the cells involved or cells in their environment with a recombinant nucleic acid molecule as claimed in any one of the preceding Claims to obtain local expression of the hybrid polypeptide or protein encoded by said nucleic acid molecule.